Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update.

Bibliographic Source(s)

Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK, American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. Endocr Pract. 2011 Jul-Aug;17(Suppl 4):1-44. [391 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Cook DM. AACE medical guidelines for clinical practice for the diagnosis and treatment of acromegaly. Endocr Pract 2004 May-Jun;10(3):213-25.

Recommendations

Major Recommendations

The levels of evidence (1-4) and the recommendation grades (A-D) are defined at the end of the "Major Recommendations" field. The best evidence level (BEL), corresponding to the best conclusive evidence found, accompanies the recommendation grade.

Executive Summary of Recommendations

Each recommendation is labeled "R" in this summary. The following recommendations are evidence-based (Grades A, B, and C) or based on expert opinion because of a lack of conclusive clinical evidence (Grade D).

Presenting Features and Assessment of Comorbidities

- R1. Patients should be queried regarding and examined for typical signs and symptoms of acromegaly, including somatic enlargement, excessive sweating, jaw overgrowth, joint pains, cardiomyopathy, carpal tunnel syndrome, sleep apnea syndrome, osteoarthropathy, diabetes mellitus, menstrual irregularities in women and sexual dysfunction in men, headache, and visual field loss (attributable to optic chiasmal compression), and diplopia (due to cranial nerve palsy) (Grade C; BEL 3).
- R2. Headaches and painful osteoarthritis are common in patients with acromegaly, and appropriate analgesic management should be considered. Definitive therapy for acromegaly is the most helpful intervention to diminish or prevent worsening of such comorbidities (Grade C; BEL 3).

- R3. The finding of hypercalcemia should prompt an evaluation for primary hyperparathyroidism and, if present, consideration of multiple endocrine neoplasia type 1 (MEN 1). Likewise, the presence of multiple family members with pituitary tumors should prompt investigation into a genetic predisposition to pituitary tumors, including MEN 1, familial acromegaly, or familial isolated pituitary adenomas (Grade C; BEL 3).
- R4. Corrective orthopedic or plastic surgical procedures should be postponed until serum concentrations of growth hormone (GH) and insulin-like growth factor-I (IGF-I) normalize (Grade C; BEL 4).
- R5. Performance of a sleep study for evaluation of sleep apnea syndrome, which is frequently associated with acromegaly, should be considered (Grade C; BEL 3).
- R6. Measurements should be performed for assessment of diabetes mellitus, and appropriate therapy should be administered if diabetes is diagnosed (Grade A; BEL 3).
- R7. Blood pressure should be measured, and appropriate therapy should be administered if hypertension is present (Grade A; BEL 3).
- R8. Cardiovascular risk status, including measurement of a lipid profile (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), should be assessed (Grade C; BEL 3).
- R9. Cardiac evaluation including an electrocardiogram and an echocardiogram may be considered, particularly if the patient has signs or symptoms suggestive of cardiac involvement, such as arrhythmias and shortness of breath (Grade C; BEL 4).
- R10. Patients with known cardiac disease should be considered for a formal cardiology consultation before a surgical procedure is performed (Grade C; BEL 4).
- R11. Although there is insufficient evidence to state that patients with acromegaly have an increased risk of colon cancer, there is evidence of an increased prevalence of colon polyps. Therefore, colonoscopy is recommended (Grade C; BEL 4).

How Is the Diagnosis Made?

- R12. Acromegaly is a clinical syndrome that, depending on its stage of progression, may not manifest with clear diagnostic features. Clinicians should think of this diagnosis in patients with two or more of the following comorbidities: new-onset diabetes, diffuse arthralgias, new-onset or difficult-to-control hypertension, cardiac disease including biventricular hypertrophy and diastolic or systolic dysfunction, fatigue, headaches, carpal tunnel syndrome, sleep apnea syndrome, diaphoresis, loss of vision, colon polyps, and progressive jaw malocclusion (Grade A; BEL 1).
- R13. A serum IGF-I level, if accompanied by a large number of results from age- and sex-matched normal subjects, is a good tool to assess integrated GH secretion and is excellent for diagnosis, monitoring, and especially screening. A random IGF-I value (a marker of integrated GH secretion) should be measured for diagnosis and for monitoring after a therapeutic intervention (Grade B; BEL 2).
- R14. Serum GH assays are not standardized and should not be used interchangeably. Multiple samples, random GH, and GH after glucose administration have considerable variability and are useful, but they must be used in the clinical context (Grade C; BEL 3).
- R15. A GH value <1 ng/mL after an oral glucose tolerance test (OGTT) (75 g of glucose orally followed by GH measurements every 30 minutes for 120 minutes) is considered normal (Grade C; BEL 3).
- R16. This panel suggests that the serum GH nadir after glucose administration be lowered to 0.4 ng/mL to increase the sensitivity of testing (Grade D; BEL 4).
- R17. Currently, there are insufficient data to recommend additional testing with insulin-like growth factor-binding protein-3 measurement or use of a thyrotropin-releasing hormone test (which can lead to a paradoxical increase in GH levels in patients with acromegaly) (Grade A; BEL 1).

Further Evaluation After Diagnosis of Acromegaly

- R18. Once a biochemical diagnosis of acromegaly has been made, a magnetic resonance imaging (MRI) scan of the pituitary gland (the physician should order a dedicated pituitary MRI with and without use of contrast medium) should be performed because a pituitary GH-secreting adenoma is the cause in most cases. A computed tomographic scan of the pituitary offers less anatomic detail and is not suggested, but it may be necessary if the patient has a contraindication for MRI, such as the presence of a cardiac pacemaker (Grade B; BEL 1).
- R19. Visual field testing should be performed if there is optic chiasmal compression noted on the MRI or if the patient has complaints of reduced peripheral vision (Grade A; BEL 1).
- R20. Further biochemical testing should include a serum prolactin level (to evaluate for hyperprolactinemia) and assessment of anterior and posterior pituitary function (for potential hypopituitarism) (Grade A; BEL 1).
- R21. All patients should undergo a comprehensive medical history, physical examination, and appropriate laboratory testing (Grade C; BEL 4).

What Are the Therapeutic Options?

- R22. There should be a thorough discussion with the patient regarding the risks and benefits of surgical, medical, and radiotherapeutic

options (Grade C; BEL 4).

- R23. The pros and cons of pituitary surgery should be discussed, with emphasis on the value of surgical intervention as the primary therapy in most patients because it is the most effective option for inducing rapid and complete biochemical cure of acromegaly in patients who meet surgical criteria (Grade C; BEL 3).
- R24. The pros and cons of primary medical therapy should be discussed, particularly in those patients who have a tumor that cannot be completely removed surgically, who have no compressive tumor effects, who are poor surgical candidates, or who have a preference for medical management (Grade C; BEL 3).
- R25. The pros and cons of radiation therapy (RT) should be discussed, with an emphasis on its use as adjuvant treatment, the potential efficacy, and the long-term side effects (Grade C; BEL 3).
- R26. Financial counseling should be provided regarding the various therapeutic options (Grade C; BEL 4).

What Are the Goals of Therapy?

- R27. There should be a thorough discussion with the patient regarding the goals of therapy, which include normalization of biochemical variables, reversal of mass effects of the tumor, improvement in signs, symptoms, and comorbidities of the disease, and minimization of long-term mortality risk (Grade B; BEL 3).
- R28. Treatment goals include assessment and management of the comorbidities, such as aggressive control of lipid abnormalities, type 2 diabetes mellitus, obstructive sleep apnea, arthritic complications, and cardiac dysfunction as well as surveillance for colon polyps (Grade C; BEL 2).

Therapeutic Options

- R29. There is sufficient evidence for recommending pituitary surgery as the primary treatment in patients with microadenomas and in patients with macroadenomas that are associated with local mass effects or are enclosed and potentially curable surgically because surgery can lead to durable control of the tumor mass and associated biochemical effects (Grade B; BEL 2).
- R30. In most patients, medical therapy is used as adjuvant treatment in the setting of persistent disease despite surgical intervention (Grade B; BEL 2).
- R31. A role of primary medical therapy, especially with somatostatin analogues (SSAs), has been suggested in patients with macroadenomas who have no local mass effects and have a minimal chance of surgical cure (because of extrasellar extension of the tumor, especially into the cavernous sinus) or in patients who are poor surgical candidates or who prefer medical treatment (Grade B; BEL 3).
- R32. RT is recommended as adjuvant treatment in patients with active disease despite surgery and medical therapy or in patients who prefer RT in light of the cost of long-term medical treatment (Grade C; BEL 3).

Surgery

- R33. There is sufficient evidence linking surgical experience (number of pituitary surgical procedures performed) with surgical cure rate as well as morbidity and mortality (Grade A; BEL 2).
- R34. There is sufficient evidence to recommend surgery as the primary therapy for all patients with microadenomas (Grade A; BEL 2).
- R35. Surgery is indicated for all patients with a macroadenoma and mass effects, including visual loss (Grade A; BEL 1).
- R36. There is sufficient evidence to recommend surgery as the primary therapy for all patients who have macroadenomas with a high predicted chance for cure (that is, no invasion of local structures such as the cavernous sinus) (Grade A; BEL 2).
- R37. In the patients with macroadenomas that are not likely to be cured with surgery, and without compressive effects on local structures, surgery may be recommended for debulking to improve the response to subsequent medical therapy or RT. There should be a thorough discussion with the patient regarding the use of primary medical therapy as an alternative in this setting (Grade B; BEL 3).

How Should Patients Be Prepared for Surgery?

- R38. The preoperative evaluation must include a comprehensive medical history, physical examination, and appropriate laboratory testing (Grade C; BEL 4).
- R39. Laboratory testing should include an evaluation for hypopituitarism, and the hormone axes, particularly adrenal and thyroid, should be replaced as indicated (Grade C; BEL 4).
- R40. A role for medical therapy with SSAs preoperatively has been suggested to reduce surgical risk, although further studies are necessary to support general use (Grade C; BEL 4).
- R41. A role for presurgical medical therapy with SSAs to improve biochemical outcomes with surgery has been suggested, although further studies are needed to support general use (Grade B; BEL 2).
- R42. Consideration should be given to careful perioperative airway management because patients with acromegaly often have a compromised airway (Grade C; BEL 3).

- R43. Cardiovascular risk assessment should be performed preoperatively in accordance with standard protocol. Routine echocardiography is not recommended preoperatively, although a role for echocardiography may be suggested, depending on attributable signs and symptoms (Grade C; BEL 4).

Management After Surgery

- R44. Postoperative management should include monitoring for electrolyte abnormalities, including diabetes insipidus and syndrome of inappropriate secretion of antidiuretic hormone, for up to 2 weeks (Grade C; BEL 3).
- R45. In the postoperative setting, the presence of diuresis may reflect obligate natriuresis after a rapid reduction in GH and IGF-I values (Grade C; BEL 3).
- R46. Adrenal function should be monitored and replaced as appropriate (Grade C; BEL 3).
- R47. It is recommended that a fasting GH level be measured early postoperatively; a postoperative day 1 GH level less than 2 ng/mL correlates with long-term remission. An OGTT can be performed 1 to 2 weeks after surgery for further diagnostic confirmation, although this procedure is not generally performed at this point (Grade C; BEL 2).
- R48. A serum IGF-I level should be remeasured at 12 weeks; a normal IGF-I value is consistent with surgical remission (Grade C; BEL 2).
- R49. A repeated OGTT may be performed at 12 weeks; a GH value <1 ng/mL is consistent with surgical remission (Grade C; BEL 2).
- R50. This panel suggests that the serum GH nadir after glucose administration be lowered to 0.4 ng/mL to increase the sensitivity of testing (Grade D; BEL 4).
- R51. Repeated imaging with an MRI scan should be performed at 12 weeks after surgery to assess for residual tumor and establish a postoperative baseline (Grade C; BEL 3).
- R52. Repeated pituitary hormone testing, including the thyroid and gonadal axes, should be performed at 6 to 12 weeks postoperatively in order to assess pituitary function and the need for hormone replacement therapy (Grade C; BEL 3).
- R53. If the repeated serum IGF-I value is reduced from baseline but still elevated at 12 weeks, repeated testing in another 9 to 12 weeks should be considered to determine whether there may be delayed biochemical normalization, before proceeding with potential surgical reexploration, medical therapy, or RT (Grade C; BEL 3).
- R54. For patients who use a nasal continuous positive airway pressure (CPAP) device for management of sleep apnea syndrome, the CPAP device is generally withheld postoperatively for a temporary period, as recommended by the neurosurgeon and sleep specialist (Grade C; BEL 4).

Medical Therapy

- R55. Medical therapy is appropriate as adjuvant treatment in patients with residual disease after surgery (Grade A; BEL 2).
- R56. There are three classes of medical therapy: dopamine agonists, SSAs, and a GH receptor antagonist (Grade A; BEL 1).
- R57. There should be a thorough discussion with the patient regarding the risks and benefits of each medication. This discussion should include financial counseling, and the physician should be able to provide clinical material for information on the medications as well as their costs (Grade A; BEL 2).

Dopamine Agonists

- R58. There are two dopamine agonists, cabergoline and bromocriptine, available for patients in the United States (Grade A; BEL 1).
- R59. Cabergoline may be more effective and better tolerated than bromocriptine (Grade C; BEL 3).
- R60. Dopamine agonists may be considered as first-line medical therapy because these agents are orally administered and relatively inexpensive in comparison with the other medical therapy options (Grade C; BEL 3).
- R61. Dopamine agonists may be considered particularly in patients with mild biochemical activity, such as in the setting of modestly elevated serum IGF-I levels in the absence or concomitant presence of SSA therapy (Grade B; BEL 3).
- R62. The response of GH to cabergoline is not clearly demonstrated to be related to the presence or absence of hyperprolactinemia (Grade C; BEL 3).
- R63. Patients should be counseled about the potential side effects of dopamine agonists, including gastrointestinal upset, orthostatic hypotension, headache, and nasal congestion (Grade A; BEL 1).
- R64. Patients should be counseled that cabergoline, when administered in high doses to patients with Parkinson disease, has been associated with echocardiographically evident valve abnormalities. The clinical effect of this finding in patients with acromegaly is unclear (Grade C; BEL 3).
- R65. Repeated GH, prolactin, and IGF-I levels should be determined 4 to 6 weeks after each dose change for a dopamine agonist (Grade B; BEL 3).

Somatostatin Analogues

- R66. There are two long-acting, depot SSAs available: octreotide LAR (long-acting release, administered as an intramuscular injection) and lanreotide Autogel (administered as a deep subcutaneous depot injection) (Grade A; BEL 1).
- R67. A 2-week trial of octreotide is recommended before institution of octreotide LAR therapy (based on the U.S. package insert), although this panel feels that a single test dose to rule out a severe reaction is sufficient (Grade D; BEL 3).
- R68. SSAs are effective in normalizing IGF-I and GH levels in approximately 55% of patients. The clinical and biochemical responses to SSAs are inversely related to tumor size and degree of GH hypersecretion. Octreotide LAR and lanreotide Autogel have similar efficacy profiles (Grade B; BEL 2).
- R69. SSAs reduce pituitary tumor size modestly in approximately 25% to 70% of patients, depending on whether they are used as adjuvant or de novo therapy, respectively. Patients should be counseled that, although tumor shrinkage can occur, SSAs should not be relied on for decompression of local structures in the presence of mass effects (Grade B; BEL 3).
- R70. Patients should be counseled about the potential side effects of SSAs, including gastrointestinal upset, malabsorption, constipation, gallbladder disease, hair loss, and bradycardia. It is not recommended that patients have close radiologic imaging surveillance for symptomatic gallbladder disease, but patients should be queried about potential symptoms during follow-up appointments. Octreotide LAR and lanreotide Autogel have similar side effect profiles (Grade B; BEL 2).
- R71. In patients with an inadequate response to SSAs, the addition of cabergoline or pegvisomant may be effective for further lowering of GH or IGF-I levels (or both) (Grade B; BEL 3).
- R72. The short-acting subcutaneously administered SSA octreotide is effective and may be used, especially in the setting of financial constraints or the need for rapid onset of action (Grade C; BEL 3).

GH Receptor Antagonist

- R73. Pegvisomant is a GH receptor antagonist that competes with endogenous GH for its receptor and prevents functional dimerization and signal transduction by the GH receptor (Grade A; BEL 2).
- R74. Pegvisomant is highly effective in normalizing IGF-I values (>90%), including patients who are partially or completely resistant to other medical therapies (Grade A; BEL 2).
- R75. Pegvisomant is effective at improving glucose homeostasis in patients with associated diabetes mellitus (Grade C; BEL 2).
- R76. Pegvisomant is often used as a medical therapy in patients with inadequate response to or tolerability of SSAs (Grade A; BEL 2).
- R77. Patients should be counseled that pegvisomant is administered as a subcutaneous injection daily, although alternative protocols, including twice-a-week or once-a-week administration, have been suggested in specific patients (Grade B; BEL 3).
- R78. Patients should be counseled about the side effects of pegvisomant, including flulike illness, allergic reactions, and increase in liver enzymes. Therefore, serial monitoring of results of liver function tests (LFTs) is suggested at monthly intervals for the first 6 months, quarterly for the next 6 months, and then biannually. Patients with elevated baseline results of LFTs need more frequent monitoring (Grade B; BEL 3).
- R79. Patients should be counseled that tumor enlargement has been infrequently associated with use of pegvisomant. Therefore, serial monitoring with pituitary MRI scans is suggested (Grade C; BEL 3).
- R80. Pegvisomant therapy may be effective regardless of baseline tumor size or degree of GH hypersecretion (Grade B; BEL 2).
- R81. Because endogenous GH levels increase with pegvisomant administration and pegvisomant may be cross-measured in GH assays, serum GH levels are not specific and should not be monitored in patients receiving pegvisomant (Grade A; BEL 2).

Combination Therapy

- R82. In patients with a partial response to SSA therapy, the addition of cabergoline may be useful for further lowering of GH or IGF-I levels (Grade C; BEL 3).
- R83. In patients with a partial response to SSA therapy, the addition of daily, weekly, or twice weekly pegvisomant may be beneficial (Grade C; BEL 3).

Radiation Therapy

- R84. Pituitary RT in acromegaly should be considered an adjunctive treatment in patients not fully responding to surgical or medical treatments (or both) (Grade C; BEL 4).
- R85. Because RT may lead to normalization of biochemical indices of acromegaly, this modality may be used in an effort to limit lifelong use of GH and IGF-I suppressive medical therapy (Grade C; BEL 4).
- R86. Patients may be counseled about the options of RT, including conventional fractionated RT versus stereotactic radiosurgery, which can be administered by means of gamma knife, proton beam, CyberKnife, or a linear accelerator (Grade C; BEL 4).
- R87. Because of the technical advances and convenience, stereotactic radiosurgery may be considered the preferred mode of RT over conventional RT in patients with acromegaly, unless the technique is not available, there is substantial residual tumor burden, or the tumor is too close (<5 mm) to the optic chiasm (Grade C; BEL 4).

- R88. Patients should be counseled that the benefits of RT on GH hypersecretion may be delayed, up to years, and medical therapy will be needed until the radiation effect is sustained. Intermittent withdrawal of medical therapy will be necessary in order to assess GH secretion (Grade C; BEL 4).
- R89. Patients should be counseled that serial pituitary function follow-up is necessary to evaluate for hypopituitarism. This follow-up includes assessment of adrenal, thyroid, and gonadal function, testing that should be performed at least annually (Grade B; BEL 2).

Acromegaly and Pregnancy

- R90. In a pregnant patient with acromegaly, biochemical monitoring with measurement of GH or IGF-I levels is of limited use (Grade B; BEL 3).
- R91. Serial visual field monitoring should be performed during pregnancy, at intervals dictated by the tumor size and location before pregnancy (Grade C; BEL 3).
- R92. MRI scans should not be routinely performed during pregnancy unless there is evidence of new or worsening visual field compromise. If performed, the MRI scan should be done without administration of a contrast agent (Grade A; BEL 1).
- R93. In pregnant patients who have tumor growth with chiasmal compression and visual field compromise, transsphenoidal surgery should be considered (Grade A; BEL 1).
- R94. Medical therapy with a long-acting SSA should be discontinued 2 to 3 months before a planned pregnancy, depending on the clinical status of the patient (Grade D; BEL 3).
- R95. If the patient conceives while receiving SSA therapy, she should have a discussion with her physician about discontinuing the SSA, with further monitoring as described in R89 (Grade D; BEL 3).
- R96. Institution of medical therapy should be considered during pregnancy if there is suggestive evidence of worsening disease (Grade D; BEL 3).

Approach to Gigantism in Children and Adolescents

- R97. Gigantism is a rare clinical syndrome that is associated with dramatic linear growth acceleration (Grade A; BEL 1).
- R98. A random serum IGF-I value, normalized for age and sex, should be measured for diagnosis; an elevated IGF-I value is consistent with the diagnosis (Grade B; BEL 2).
- R99. Once a biochemical diagnosis of gigantism has been made, an MRI scan of the pituitary gland (the physician should order a dedicated pituitary MRI with and without use of contrast medium) should be performed because a pituitary GH-secreting adenoma is the cause in most cases (Grade B; BEL 1).
- R100. Visual field testing should be performed if there is optic chiasmal compression noted on the MRI or the patient has complaints of reduced peripheral vision (Grade A; BEL 1).
- R101. The goals of therapy are to control the biochemical variables and reduce tumor volume, as in acromegaly. Another goal of therapy is to control the accelerated linear growth (Grade A; BEL 1).
- R102. Transsphenoidal surgery is the primary treatment, where possible (Grade C; BEL 3).
- R103. Use of medical therapy as an adjunctive treatment after incomplete surgery is similar to that with adults (Grade C; BEL 4).
- R104. In patients with gigantism, RT is often not used (Grade C; BEL 3).

How Should Medical Comorbidities Be Monitored?

- R105. Any corrective surgical procedure, such as maxillofacial correction of dental malocclusion, should be postponed until GH and IGF-I levels normalize for at least 6 months (Grade D; BEL 4).
- R106. Patients should be monitored for signs and symptoms of carpal tunnel syndrome, and directed care, including a release procedure, should be considered for persistent or progressive symptoms (Grade C; BEL 3).
- R107. Arthropathy should be managed aggressively with physical therapy, systemic or intra-articular anti-inflammatory medications, and consideration of joint replacement, when appropriate (Grade C; BEL 3).
- R108. The presence of hypercalcemia should prompt an evaluation for primary hyperparathyroidism and, if present, consideration of MEN 1 (Grade B; BEL 3).
- R109. Bone densitometry should be performed in patients with a history of hypogonadism or fracture. If osteoporosis is present and does not improve with correction of hypogonadism, hypercalcemia, GH and IGF-I excess, or any combination of these factors, antiresorptive therapy should be considered (Grade C; BEL 3).
- R110. Formal overnight polysomnography or home overnight oximetry (as a screening test for sleep apnea) followed by formal overnight polysomnography should be performed if symptoms are suggestive in patients with either active or biochemically controlled acromegaly (Grade C; BEL 3).
- R111. Standard therapy should be used for patients with left ventricular hypertrophy, impaired cardiac systolic and diastolic function,

arrhythmias, conduction abnormalities, valvular heart disease, or ischemic heart disease (Grade C; BEL 4).

- R112. Routine echocardiography should be considered in patients who have evidence of left ventricular hypertrophy by electrocardiography or who are symptomatic with shortness of breath (Grade C; BEL 3).
- R113. Blood pressure should be monitored because hypertension may persist despite biochemical control of acromegaly (Grade C; BEL 3).
- R114. All patients should be monitored for evidence of glucose intolerance or overt type 2 diabetes mellitus, and corrective measures should be taken as needed (Grade C; BEL 3).
- R115. In patients in whom SSA therapy worsens glucose control, reduction of the SSA dose, addition of or substitution with a GH receptor antagonist, or diabetes management with glucose-lowering agents should be considered (Grade C; BEL 3).
- R116. Goals for high-risk cardiac patients should be adopted, including blood pressure less than 130/80 mm Hg and hemoglobin A1c less than 6.5% (Grade C; BEL 2).
- R117. Colonoscopy should be performed after diagnosis of acromegaly. Patients with polyps at screening or with persistently elevated IGF-I levels should undergo follow-up colonoscopy. Other patients should undergo follow-up colonoscopy, with a schedule based on current general recommendations (Grade C; BEL 4).
- R118. Standard screening guidelines for other cancers should be rigorously followed (Grade B; BEL 4).
- R119. In patients with active acromegaly and those in remission, attention to quality-of-life issues is recommended (Grade C; BEL 4).

Definitions:

Levels of Scientific Substantiation in Evidence-Based Medicine*

Level	Description	Comments
1	Prospective, randomized controlled trials—large	Data are derived from a substantial number of trials, with adequate power involving a substantial number of outcome data subjects Large meta-analyses using raw or pooled data or incorporating quality ratings Well-controlled trial at one or more centers Consistent pattern of findings in the population for which the recommendation is made (generalizable data) Compelling nonexperimental, clinically obvious evidence (for example, use of insulin in diabetic ketoacidosis); "all-or-none" indication
2	Prospective with or without randomization—limited body of outcome data	Few number of trials, small population sizes in trials Well-conducted single-arm prospective cohort study Meta-analyses are limited but are well conducted Inconsistent findings or results not representative for the target population Well-conducted case-controlled study
3	Other experimental outcome data and nonexperimental data	Nonrandomized, controlled trials Uncontrolled or poorly controlled trials Any randomized clinical trial with one or more major or three or more minor methodologic flaws Retrospective or observational data Case reports or case series Conflicting data with weight of evidence unable to support a final recommendation
4	Expert opinion	Inadequate data for inclusion in above necessitate an expert panel's synthesis of the

Level	Description	Comments
		literature and a consensus Experience-based Theory-driven

*Levels 1-3 represent a given level of scientific substantiation or proof. Level 4 represents unproven claims. It is the "best evidence" based on individual ratings of clinical reports that contributes to a final grade recommendation.

Grade-Recommendation Protocol Adopted by the American Association of Clinical Endocrinologists*

Grade	Description	Recommendation
A	≥1 conclusive level 1 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports Action based on strong evidence Action can be used with other conventional therapy or as "first-line" therapy
B	No conclusive level 1 publication ≥1 conclusive level 2 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports *If* the patient refuses or fails to respond to conventional therapy; must monitor for adverse effects, if any Action based on intermediate evidence Can be recommended as "second-line" therapy
C	No conclusive level 1 or 2 publication ≥1 conclusive level 3 publications demonstrating benefit >> risk *or* No risk at all and no benefit at all	Action recommended for indications reflected by the published reports *If* the patient refuses or fails to respond to conventional therapy, provided there are no significant adverse effects; "no objection" to recommending their use *or* "No objection" to continuing their use Action based on weak evidence
D	No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit	Not recommended Patient is advised to discontinue use Action not based on any evidence

*The final recommendation grades are determined by the primary writers by consensus based on (1) "best evidence" ratings and (2) subjective factors (see the "Description of Methods to Formulate the Recommendations" field).

Clinical Algorithm(s)

The original guideline document contains an algorithm on the approach to therapy in patients with acromegaly.

Scope

Disease/Condition(s)

Acromegaly

Other Disease/Condition(s) Addressed

- Arrhythmias
- Arthropathy
- Carpal tunnel syndrome
- Conduction abnormalities
- Diabetes mellitus
- Headaches
- Hypercalcemia
- Hypertension
- Impaired cardiac systolic and diastolic function
- Ischemic heart disease
- Left ventricular hypertrophy
- Osteoporosis
- Sleep apnea
- Valvular heart disease

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Pediatrics

Surgery

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To update clinicians regarding all aspects in the current management of acromegaly and to use methods of current clinical practice guidelines to support the recommendations

Target Population

Patients with suspected or confirmed acromegaly

Interventions and Practices Considered

Diagnosis/Evaluation

1. Assessment of clinical signs and symptoms of acromegaly
2. Assessment of comorbidities
3. Sleep study for sleep apnea syndrome
4. Assessment for diabetes
5. Blood pressure measurement
6. Cardiovascular risk assessment and cardiac evaluation, including lipid profile, electrocardiogram, echocardiogram
7. Colonoscopy
8. Laboratory measurement of serum levels of insulin-like growth factor-I (IGF-I), growth hormone (GH), prolactin
9. Magnetic resonance imaging scan of pituitary gland
10. Visual field testing

Management/Treatment

1. Counseling patient about treatment options, risks, benefits, and financial considerations
2. Pituitary surgical therapy and postoperative management
3. Pharmacologic therapy (somatostatin analogues [octreotide long-acting release (LAR), lanreotide Autogel]; growth hormone receptor antagonists [pegvisomant]; dopamine agonists [cabergoline, bromocriptine])
4. Combination therapy (somatostatin analogue + cabergoline; somatostatin analogue + pegvisomant)
5. Pituitary radiation therapy (conventional fractionated, stereotactic)
6. Monitoring and treating comorbidities
7. Special considerations for acromegaly in pregnancy and gigantism in children and adolescents

Major Outcomes Considered

- Disease-related morbidity and mortality
- Sensitivity and specificity of diagnostic tests
- Measures of treatment efficacy, including normalization of growth hormone (GH), insulin-like growth factor-I (IGF-I) levels, clinical remission, tumor size, and tumor recurrence
- Treatment-related morbidity and mortality
- Side effects and adverse effects of treatment
- Maternal and neonatal safety
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

PubMed was searched for articles published since the last guideline in 2004. Reviews and high level references were included. Opinion papers were not included. Search terms were *acromegaly, pituitary tumor, pituitary adenoma, somatostatin analog, dopamine, pegvisomant, gigantism, and transsphenoidal surgery*.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

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2	Prospective with or without randomization—limited body of outcome data	Few number of trials, small population sizes in trials Well-conducted single-arm prospective cohort study Meta-analyses are limited but are well conducted Inconsistent findings or results not representative for the target population Well-conducted case-controlled study
3	Other experimental outcome data and nonexperimental data	Nonrandomized, controlled trials Uncontrolled or poorly controlled trials Any randomized clinical trial with one or more major or three or more minor methodologic flaws Retrospective or observational data Case reports or case series Conflicting data with weight of evidence unable to support a final recommendation

Level	Description	Comments
4	Expert opinion	Inadequate data for inclusion in above necessitate an expert panel's synthesis of the literature and a consensus Experience-based Theory-driven

*Levels 1-3 represent a given level of scientific substantiation or proof. Level 4 represents unproven claims. It is the "best evidence" based on individual ratings of clinical reports that contributes to a final grade recommendation.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Transparency: Levels of Scientific Substantiation

All clinical data that are incorporated in these clinical practice guidelines (CPG) have been evaluated in terms of levels of scientific substantiation (evidence levels [EL]; see the "Rating Scheme for the Strength of Evidence" field). This evidence rating system has one minor modification in comparison with the original American Association of Clinical Endocrinologists protocol (EL 4) in that level 2 (EL 2) prospective studies now may be randomized or nonrandomized to allow for well-designed cohort studies. This modification was incorporated because it is difficult to perform well-controlled, randomized clinical trials in surgery, unlike what physicians have been accustomed to in pharmaceutical trials. Another point worth mentioning is that when consensus statements are cited, even if based on a synthesis of evidence as in a published "evidence-based report," then an evidence level 4 (EL 4) is assigned. Clinical references have been assigned an evidence rating, which is provided in brackets at the end of the citation in both the Appendix and Reference sections of the original guideline document. The "best evidence" level (BEL) corresponds to the best conclusive evidence found. The BEL accompanies the recommendation Grade and maps to the text in the Appendix section of the original guideline document, where transparency is paramount.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Transparency: Recommendation Grades

Final recommendation grades incorporate evidence level (EL) ratings (see the "Rating Scheme for the Strength of Recommendations" field), and in situations in which there is no clinical evidence, various subjective factors are considered: physician preferences, costs, risks, and regional availability of specific technologies and expertise. Hence, recommendation grades are generally based on strong best evidence level (BEL) (Grade A; BEL 1), intermediate BEL (Grade B; BEL 2), weak BEL (Grade C; BEL 3), or subjective factors when there is no clinical evidence, inconclusive clinical evidence, or contradictory clinical evidence (Grade D; BEL 4). All recommendations result from a consensus among the American Association of Clinical Endocrinologists primary writers and influenced by input from reviewers. If subjective factors take priority over the BEL based on the expert opinion of the task force members, then this is described explicitly. Thus, some recommendations may be "upgraded" or "downgraded" according to explicitly stated subjective factors. Furthermore, the correctness of the recommendation Grades and EL is subject to review at several levels. In addition, recommendation Grades are assigned only if a specific action is recommended. The action may be ordering a particular diagnostic test, using a particular drug, performing a particular procedure, or adhering to a particular algorithm.

Shortcomings of this evidence-based method in this clinical practice guideline are as follows: (1) relative paucity of strong (EL 1 and 2) scientific data, leaving the majority of recommendations based on weaker, extant EL 3 data and EL 4 consensus opinion; (2) potential subjectivity of the primary writers when weighing positive and negative, or epidemiologic versus experimental, data to arrive at an evidence-based recommendation

grade or consensus opinion; (3) potential subjectivity of the primary writers when weighing subjective attributes, such as cost-effectiveness and risk-benefit ratios, to arrive at an evidence-based recommendation grade or consensus opinion; (4) potentially incomplete review of the literature by the primary writers despite extensive diligence; and (5) bias in the available publications, which originate predominantly from experienced pituitary endocrinologists and neurosurgeons and therefore may not reflect the experience at large. These shortcomings have been addressed by the primary writers through an a priori method and multiple levels of review by a large number of experts.

Rating Scheme for the Strength of the Recommendations

Grade-Recommendation Protocol Adopted by the American Association of Clinical Endocrinologists*

Grade	Description	Recommendation
A	≥1 conclusive level 1 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports Action based on strong evidence Action can be used with other conventional therapy or as "first-line" therapy
B	No conclusive level 1 publication ≥1 conclusive level 2 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports *If* the patient refuses or fails to respond to conventional therapy; must monitor for adverse effects, if any Action based on intermediate evidence Can be recommended as "second-line" therapy
C	No conclusive level 1 or 2 publication ≥1 conclusive level 3 publications demonstrating benefit >> risk *or* No risk at all and no benefit at all	Action recommended for indications reflected by the published reports *If* the patient refuses or fails to respond to conventional therapy, provided there are no significant adverse effects; "no objection" to recommending their use *or* "No objection" to continuing their use Action based on weak evidence
D	No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit	Not recommended Patient is advised to discontinue use Action not based on any evidence

*The final recommendation grades are determined by the primary writers by consensus based on (1) "best evidence" ratings and (2) subjective factors (see the "Description of Methods to Formulate the Recommendations" field).

Cost Analysis

Acromegaly is a disease with a substantial economic burden. Longitudinal assessment of the economic costs relative to clinical and biochemical outcomes was examined for a 4-year period in 53 Canadian patients. The mean annual cost per patient in Canadian dollars was $8,111 (95% confidence interval, $5,848 to $10,374). Growth hormone (GH)- and insulin-like growth factor-I (IGF-I)-reducing medications constituted the largest component (nearly 38%) of the overall cost of management. It should be emphasized that although surgical costs per patient were high ($2,800 to $9,200), the 4-year mean annual cost was approximately $2,400 less than the cost of medications. Furthermore, treatment of patients

with macroadenomas costs considerably more annually ($11,425) than treatment of those with microadenomas ($4,442); this fact emphasizes the importance of earlier diagnosis. In addition, a recent study indicated that, to be cost-effective, the price of pegvisomant should be reduced by a third. Although these are considerable costs, they are not significantly higher than those associated with other chronic diseases. Short-acting somatostatin analogues (SSAs), administered as subcutaneous injections, are appreciably less expensive than long-acting depot preparations and may be considered in the setting of financial constraints. There has also been consideration that the combination of the GH receptor antagonist pegvisomant and an SSA may result in lower doses of each medication, eventuating in lower annual costs. There is a significant cost differential between cabergoline and SSAs. In the United States, the annual retail cost of generic cabergoline (assuming a dosage of 2 mg weekly) is approximately a fifth that of Sandostatin long-acting release (LAR) (assuming a dosage of 20 mg monthly). Cost is one of the factors that is considered for use of cabergoline as first-line medical therapy in patients with moderate disease.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Recommendations were reviewed by a large number of experts. All recommendations were influenced by input from reviewers.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and treatment of acromegaly

Potential Harms

Cardiopulmonary Complications and Anesthesia-Related Risks of Surgical Treatment

Patients with acromegaly are at increased risk of anesthesia-related complications including hemodynamic changes, with a significantly higher incidence of difficulty with intubation because of laryngeal and pharyngeal soft tissue swelling and vocal cord swelling. The oropharyngeal swelling and macroglossia result in an increased frequency of sleep apnea syndrome, which has been reported in 20% to 80% of this population. Sleep apnea itself is associated with an increased risk of coronary artery disease and hypertension and may complicate both the preoperative and the postoperative status of the patient and delay extubation.

Medical Therapy

- Side effects of dopamine agonists include gastrointestinal upset, nasal congestion, fatigue, orthostatic hypotension, and headache. Cabergoline may be better tolerated than bromocriptine. When administered in higher doses (for example, more than 3 mg daily) in patients with Parkinson disease, cabergoline has been associated with an increased risk of echocardiographically evident valvular abnormalities.
- Early adverse events associated with use of somatostatin analogues (SSAs) include transient abdominal cramps and malabsorptive diarrhea. Long-term use of SSAs is also associated with an increased incidence of gallbladder sludge and gallstone formation, but these effects are not typically of clinical significance. Less frequently, hair loss or, even more uncommonly, bradycardia or constipation is experienced. SSAs appear to cause a moderate impairment of glucose tolerance, and overt diabetes mellitus may be infrequently detected. In patients in whom

SSA therapy worsens glucose control, reduction of the SSA dose, addition of or substitution with a growth hormone (GH) receptor antagonist, or diabetes management with glucose-lowering agents should be considered.

- Although several cases of tumor growth during pegvisomant therapy have been reported, observational studies have shown this to be an uncommon finding that may reflect the presence of more aggressive tumors or may possibly be a rebound effect due to withdrawal of SSAs. Therefore, patients receiving this GH receptor antagonist require close observation with serial magnetic resonance imaging (MRI) scans, such as at 6-month intervals during the first year of management and then at annual intervals. Pegvisomant should probably not be the first-line pharmacologic therapy in patients with large macroadenomas or tumors of any size near the optic chiasm. Pegvisomant therapy is associated with abnormal results of liver function tests (LFTs), and in the German Pegvisomant Observational Study, transaminase levels greater than three times normal were noted in 5.2% of patients. Of note, 58% of these patients had normalization of transaminase levels with continued treatment, and another 33% had normalization after discontinuation of pegvisomant therapy. These transaminase elevations are usually asymptomatic, and often transient and self-limiting, despite continued administration of pegvisomant. Nevertheless, results of LFTs need to be monitored regularly in patients receiving pegvisomant treatment. Other more uncommon side effects include a flulike illness, local allergic reactions, and local lipohypertrophy.
- In some patients SSA therapy can worsen glucose control by inhibiting insulin secretion, in which case alternative therapies, such as pegvisomant, should be considered.

Radiation Therapy (RT)

- There appears to be an increased incidence of side effects, including hypopituitarism, visual deficit, and radionecrosis, after combination RT procedures. There is a distinct need for further studies, however, in order to provide a clearer perspective.
- Complications of RT: The main limitations for RT in patients with acromegaly are the development of hypopituitarism and long-term safety. Fractionated RT may be associated with an increased risk of cerebrovascular disease, depending on the dose delivered. There is also a concern regarding the rare but feared loss of vision in patients undergoing RT. The risk of cerebrovascular disease in patients with acromegaly undergoing RT appears to be increased in comparison with those treated otherwise. Radiation-induced secondary tumors and radionecrosis have been reported in ≤2% of patients undergoing conventional RT. In a review among 1,567 patients treated with gamma knife radiosurgery, 0.8% developed radionecrosis. About half of these patients had been treated previously with conventional irradiation. The risk of cognitive deficit after RT continues to be controversial. See section 10.2.3 of the original guideline document for additional detail on complications associated with RT.
- RT is used less frequently in gigantism than in acromegaly because of the long-term consequences of irradiation during a longer life expectancy, including hypopituitarism and possible cognitive dysfunction.

Acromegaly and Pregnancy

- An increased incidence of prematurity (37% versus 8%) was observed in the offspring of patients with acromegaly undergoing intrapartum pituitary surgery in one study. More current studies are needed to address this subject.
- In a few cases of pregnant patients given SSA therapy, the resultant infants were small for gestational age, although the causality was not clear.

Contraindications

Contraindications

A computed tomographic scan of the pituitary offers less anatomic detail and is not suggested, but it may be necessary if the patient has a contraindication for magnetic resonance imaging (MRI), such as the presence of a cardiac pacemaker.

Qualifying Statements

Qualifying Statements

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. Guideline developers encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these

guidelines must be made in light of local resources and individual patient circumstances.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK, American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. Endocr Pract. 2011 Jul-Aug;17(Suppl 4):1-44. [391 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

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Financial Disclosures/Conflicts of Interest

Disclosure

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Dr. Laurence Katznelson reports that he has received speakers' bureau honoraria from IPSEN and advisory board honoraria and research grant support from Novartis AG.

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Dr. John L. D. Atkinson reports that he does not have any relevant financial relationships with any commercial interests.

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Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Cook DM. AACE medical guidelines for clinical practice for the diagnosis and treatment of acromegaly. Endocr Pract 2004 May-Jun;10(3):213-25.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site .

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 245 Riverside Avenue, Suite 200, Jacksonville, FL 32202

Availability of Companion Documents

The following is available:

- American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines - 2010 update. Endocrine Pract 2010;16:270-283. Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site .

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 245 Riverside Avenue, Suite 200, Jacksonville, FL 32202

Patient Resources

None available

NGC Status

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